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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/960,665	09/21/2001	Neal Rosen	MSK.P-038-2	5586

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EXAMINER	
KIFLE, BRUCK	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 12/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/960,665	ROSEN ET AL.	
	Examiner	Art Unit	
	Bruck Kifle, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's amendments and remarks filed 10/05/05 have been received and reviewed. Claims 35-66 are now pending in this application.

Claim Rejections - 35 USC § 112

Claims 35-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the geldanamycin dimers, wherein the linkers are $(CH_2)_{4-12}$ and linked at the 17-carbon of each geldanamycin, to treat breast cancer, does not reasonably provide enablement for "a chemical compound comprising first and second hsp-binding moieties which bind to the pocket of hsp90 with which ansamycin antibiotics bind, leading to degradation in proteasomes of a subset of proteins requiring hsp90 for conformational maturation, said binding moieties being connected to one another by a linker, wherein the first and second hsp-binding moieties each retain the ability in the chemical compound to bind to the pocket of hsp90 and lead to degradation in proteasomes of a subset of proteins requiring hsp90 for conformational maturation." The basis of this rejection is the same as given in the previous office action and is incorporated herein fully by reference.

Applicants argue that "they are not responsible for enabling future inventions" and that the examiner "has not alleged that there would be any difficulty in making a chemical compound with two presently known HSP-90 binding moieties connected by a linker or with testing the compound to see if the moieties retained the ability to bind to HSP-90."

However, there is no allegation that Applicants enable future inventions. The problem with the claim is determining the compound claimed.

Claim 36 limits only one of the moieties as geldanamycin and the linker as being connected to the 17-carbon of this geldanamycin.

Claims 35-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling as a method of treating HER-2 expressing cancer using geldanamycin dimer linked by a 4-carbon chain at the 17-positions of each, does not reasonably provide enablement for treating cancers or destruction of other cells using "a chemical compound comprising first and second hsp-binding moieties which bind to the pocket of hsp90 with which ansamycin antibiotics bind leading to degradation in proteasomes of a subset of proteins requiring hsp90 for conformational maturation, said binding moieties being connected to one another by a linker, wherein the first and second hsp-binding moieties each retain the ability in the chemical compound to bind to the pocket of hsp90 and lead to degradation in proteasomes requiring hsp90 for conformational maturation." The basis of this rejection is the same as given in the previous office action and is incorporated herein fully by reference.

The specification does not enable one skilled in the art, to use the invention commensurate in scope with these claims.

See MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art. In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: The method of use claims are drawn to the destruction of cells expressing a HER-family tyrosine kinase (claims 44-52) and to a method of treating cancer (claims 53-66) comprising administering the compound of claim 35.

2) The state of the prior art: There is no general treatment for cancer and there is no correlation between the assays relied upon by applicants and the ability to treat all cancers. Thus, those assays are not sufficient to enable such claims. The remarkable advances in chemotherapy have seen the development of specific compounds to treat specific types of cancer. The great diversity of diseases falling within the "cancer" category means that it is contrary to current medical understanding that any agent (let alone a genus of compounds) could be generally effective against cancers. Different agents are used for different specific forms of cancer and no single agent is known as a treatment of every single type of cancer.

No compound has shown clinical efficacy against all cancers, thus no *in vivo* or *in vitro* assay could be validated for the identification of such a general agent. The instant specification logically lacks such assay data.

In re Buting 163 USPQ 689 establishes that even clinical tests showing that a compound found to be useful in the treatment of two types of cancers was not sufficient for a much broader range.

See for example, Sreedhar et al. (Biochimica et Biophysica Acta 1697 (2004), 233-242), a review article about inhibitors of Hsp90, Geldanamycin as one Hsp90 inhibitor (page 236) and the limitations of Hsp90 inhibition (page 239). Applicants are going far beyond what is known for the monomer to treat cancer using any compound of claim 35.

3) The predictability or lack thereof in the art: The invention is pharmaceutical in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be unpredictable. See In re Fisher 166 USPQ 18. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group where as herein no examples of a diverse nature have been made, much less tested, showing the requisite activity needed to practice the invention.

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no dosage data present to treat a host with any cancer. Only compounds that are GM dimers have been made (see page 6, Table 1) which are much closer to each other than to the remaining scope. Thus, the amount of guidance presented in the specification as to which compounds are sufficiently active to be useful for the claimed uses is nonexistent.

6) The breadth of the claims: The compounds embraced by the claims do not give a reasonable assurance that all or substantial all of them would work. See the testing done in the specification where minor structural differences result in extreme sensitivity. For example, a compound that differs only by the length of the linking carbon chain by two carbons (from 7 to 9) results in one test varies from 70 to 500. This is evidence that the compounds claimed are extremely sensitive to minor structural changes.

The claims are drawn to disorders that are not related and whose treatment using a single compound is unknown. Pancreatic cancer, for example, has proven extremely difficult to treat. Gastric cancer embraces several different types of cancers which includes, Adenocarcinomas

(cancers started in the gland cells in the stomach lining), Squamous cells cancers are cancers in the skin-like cells that are mixed with gland cells to make the stomach lining, Lymphomas, sarcomas (cancer that begins in the muscle layer of the stomach is a sarcoma) and Neuroendocrine tumours (cancers that grow in hormone producing tissues, usually in the digestive system). Treatment for each is different.

Regarding claim 44, there is no disclosed benefit taught in destroying all cells, including healthy ones, as claimed in claim 44.

7) The quantity of experimentation need would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

Claims 35-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

i) The nature of the linker is unknown. One skilled in the art cannot say which "linker" is intended. Could any one of a bond, a ring structure, a peptide, a sugar, an antibody, a cyclic peptide, etc. be a linker? In addition, in claims 37, 46 and 56, the claim language "length of 4 to 7 carbon atoms" is unclear. Are only alkylenes intended or are Applicants relying on the length

of carbon atoms. Appropriate correction is required. The linker should have distinguishing identifying characteristics defined to determine the scope. Applicants' response does not say what the linker is.

ii) The scope of the compounds claimed is undeterminable. The term "bind" in the claims is indefinite. The basis of this rejection is the same as given in the previous office action and is incorporated herein fully by reference. Applicants' arguments have been fully considered but not found persuasive. Part of the problem with the term "bind" is that this may mean simple contact (such as close proximity to each other) or covalent (chemical) bonding.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 35-66 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 4, 6 and 9-34 of copending Application No. 09/937,192. Although the conflicting claims are not identical, they are not patentably distinct from each other because these two sets of claims overlap when, for example, two geldanamycin are linked at their respective 17 positions by 1,4-butanediyldiimino.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruck Kifle, Ph.D. whose telephone number is 571-272-0668. The examiner can normally be reached Tuesdays to Fridays between 8:30 AM and 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bruck Kifle, Ph.D.
Primary Examiner
Art Unit 1624

BK
December 23, 2005